Remarks

Applicants thank the Examiner and his supervisor, Dr. Johann Richter, for reviewing the Office Action mailed January 25, 2007 and acknowledging that this Office Action was incorrectly labeled a "Final Rejection". In the Official Communication mailed July 6, 2007, the Examiner indicated that the finality of the Office Action mailed January 25, 2007 had been withdrawn.

In the Office Action mailed January 25, 2007, the Examiner indicated that claims 23-26 were allowable and claims 18-21, 28-30, and 33-35 were objected to for depending upon a rejected base claim. The Examiner also withdrew his previous rejections of claims 16, 19 and 20 under 35 U.S.C. § 103 (a) over U.S. Patent No. 6,063,910 to Debenedetti, *et al.*, and of claims 16 and 21 under 35 U.S.C. § 103 (a) over Japanese patent application 363020301 by Sugaya, *et al.* Further, the Examiner acknowledged that claims 16-18 and 22 meet the written description requirement and that claims 23-26 are definite.

Rejection Under 35 U.S.C. § 103

Claims 16, 17, 27, 31, 32, and 36 were rejected under 35 U.S.C. § 103(a) as being obvious over European Patent No. EP 0 257 915 to Boyes *et al.* ("Boyes"). Claim 22 was rejected under 35 U.S.C. § 103(a) as being obvious over Boyes in view of U.S. Patent No. 4,866,051 to Hunt *et al.* ("Hunt"). Applicants respectfully traverse these rejections to the extent that they are applied to the claims as amended.

Boyes

Claim 16

Boyes discloses microparticles formed of particular wall-forming materials and a surfactant, which encapsulate a drug to be delivered. Boyes discloses particular materials that are suitable to form inhalable microparticles. These materials are biodegradable polymeric wall materials, and include "poly(glycolic acid), poly-d,1-lactic acid copolymers thereof, copolyoxylates, polycaprolactone, and poly(lactic acid-caprolactone)" (page 3, lines 41-43).

As noted by the Examiner, Boyes does not disclose or make obvious dry microparticles that contain a lipid, hydrophilic or hydrophobic proteins or diketopiperizines (Office Action at page 6, section 13). Further, claims 18-21, which depend from claim 16, were objected to by the Examiner for depending on a rejected base claim. Claim 16 has been amended to specify that the material used to form the microparticles is a material listed in claims 18-21, i.e. alginate, chitosan, a hydrophilic or hydrophobic protein, or a lipid. The recitation of "polymers of mixed amino acids" has been deleted from claim 16, as they refer to a type of protein or peptide. Claims 17 and 21 have been canceled in view of the amendment to claim 16. Thus claim 16, as amended, specifically recites the limitations that the Examiner indicated are allowable. Therefore claim 16, as amended, is non-obvious in view of Boyes.

Further, the rejection of claim 17 is moot in view of its cancellation.

Claims 27 and 31

Independent claim 27 defines a microparticulate system for drug delivery to the pulmonary system comprising microparticles incorporating therein a therapeutic, prophylactic or diagnostic agent. Claim 27 has been amended to specify that microparticles consist essentially of a material selected from the group consisting of, poly(hydroxy acids), polyanhydrides, polyesters, polyamides, polycarbonates, polyalkylenes, polyvinyl compounds, polysiloxanes, polymers of acrylic and methacrylic acids, polyurethanes and co-polymers thereof, poly(butyric acid), poly(valeric acid), poly(lactide-co-caprolactone), polysaccharides, and copolymers and mixtures thereof. Claim 31 depends from claim 27 and further specifies the therapeutic agent.

Boyes requires the presence of a surfactant in addition to the wall forming material to delay release of the drug from the microparticle (*see e.g.* page 2, lines 37-41). Boyes explains that a problem with other inhalable formulations was that the drugs were rapidly systemically absorbed, and such formulations were not suitable for the treatment of the diseases of the respiratory system (*see* page 2, lines 7-10). In contrast, claim 27, as amended, specifies that the microparticles consist essentially of the therapeutic, prophylactic or diagnostic agent and a material selected from the listed materials. As noted in M.P.E.P. § 2111.03, the transitional phrase "consisting essentially of" "limits the scope of a claim to the specified materials or steps 'and those that do not materially affect the basic and novel characteristic(s)' of the claimed invention. (*Id.*, citing *In re Herz*, 537 F.2d 549, 551-52, 190 U.S.P.Q .461, 463 (C.C.P.A. 1976)). Therefore claim 27 as amended excludes the incorporation of a surfactant at a level that

delays release of the drug from the microparticle. Boyes teaches away from such microparticles. Claim 31 incorporates the limitations of claim 27, from which it depends. Therefore, claims 27 and 31, as amended, are non-obvious in view of Boyes.

Claims 32 and 36

Independent claim 32 was amended in a manner similar to the amendment for claim 27, discussed above. Claim 32 defines a method for drug delivery to the pulmonary system comprising administering to a patient in need of treatment an effective amount of microparticles incorporating therein a therapeutic, prophylactic or diagnostic agent. The claim has been amended to specify that microparticles consist essentially of a material selected from the group consisting of poly(hydroxy acids), polyanhydrides, polyesters, polyamides, polycarbonates, polyalkylenes, polyvinyl compounds, polysiloxanes, polymers of acrylic and methacrylic acids, polyurethanes and co-polymers thereof, poly(butyric acid), poly(valeric acid), poly(lactide-co-caprolactone), polysaccharides, and copolymers and mixtures thereof. Claim 36 depends from claim 32 and further specifies the therapeutic agent.

As noted above, Boyes requires the presence of a surfactant in addition to the wall forming material to delay release of the drug from the microparticle (*see e.g.* page 2, lines 37-41). Boyes explains that a problem with other inhalable formulations was that the drugs were rapidly systemically absorbed, and such formulations were not suitable for the treatment of the diseases of the respiratory system (*see* page 2, lines 7-10). In contrast, claim 32, as amended, specifies that the microparticles consist essentially of the therapeutic, prophylactic or diagnostic

agent and a material selected from the listed materials. Therefore claim 32, as amended, excludes the incorporation of a surfactant at a level that delays release of the drug from the microparticle. Boyes teaches away from such microparticles. Claim 36 incorporates the limitations of claim 32, from which it depends. Therefore, claims 32 and 36, as amended, are non-obvious in view of Boyes.

Boyes in combination with Hunt

Claim 22

As noted by the Examiner and discussed above, the prior art does not disclose or make obvious dry microparticle formulations that contain a lipid, hydrophilic or hydrophobic proteins or diketopiperizines, nor the materials listed in claims 18-21 (Office Action at page 6, section 13). Claim 22 has been amended to specify that the material used to form the microparticles may be alginate, chitosan, a hydrophilic or hydrophobic protein, or a lipid. Thus claim 22, as amended, specifically recites the limitations that the Examiner indicated are allowable. Therefore claim 22, as amended, is patentable.

New Claims 37-54 are non-obvious in view of the cited art

Claim 37

New claim 37 depends from claim 22 and specifies that the cartridge is suitable for use in a dry powder inhaler. Support for this amendment can be found in the specification at least at page 22, lines 31-32. As noted above, claim 22 has been amended to specify that the material used to form the microparticles may be alginate, chitosan, a hydrophilic or hydrophobic protein,

or a lipid. Thus claim 22, as amended, specifically recites the limitations that the Examiner indicated are allowable. Claim 37 includes the limitations of claim 22. Therefore new claim 37 is non-obvious in view of Boyes.

Claims 38-39

New independent claim 38 defines a method for delivery of a drug to the pulmonary system, which requires administering to a patient in need of treatment an effective amount of the microparticles defined by claim 16, as amended. Claim 39 further defines the drug as selected from a list of drugs. Support for these claims can be found in the specification at least in claims 7 and 11 as originally filed, page 6, lines 31-34, page 13, line 11, page 18, line 22, and page 20, line 27.

New independent claim 38 specifies that the material used to form the microparticles is a material listed in claims 18-21, *i.e.* alginate, chitosan, a hydrophilic or hydrophobic protein, or a lipid. Thus claim 38 and its dependent claim, claim 39, require the limitations that the Examiner indicated are allowable. Therefore claims 38 and 39 are nonobvious in view of Boyes.

Claims 40-45

New independent claim 40 defines a microparticulate system for drug delivery to the pulmonary system containing microparticles having a size range of between 0.5 and ten microns comprising an effective amount of a drug to be delivered and a diketopiperazine, wherein the microparticles release the drug at a pH of 6.0 or greater, and wherein the microparticles are in a dry powder inhaler or a container for a dry powder inhaler. New claim 41 depends from claim

40 and specifies that the microparticles consist essentially of the drug to be delivered and the diketopiperazine. Dependent claims 42-44 generally correspond with claims 24-26. Claim 45 depends from claim 44 and specifies that the drug is insulin. Support for claims 40-45 can be found in the specification at least at claims 1 and 3 as originally filed; page 6, line 2; page 14, lines 27-30 and page 15, lines 4-6; page 18, lines 5-8, 14-15, and 17-20; page 18, line 32 until page 19, line 3, and page 22, lines 31-32 and page 23, lines 3-6 and 20-23.

As noted above, Boyes discloses microparticles formed of particular wall-forming materials and a surfactant, which encapsulate a drug to be delivered. Boyes discloses particular materials that are suitable to form the microparticles. Boyes does not disclose or suggest using diketopiperazines.

Further, the Examiner indicated that claim 23 and its dependent claims, claims 24-26, were allowable. Claim 40 defines a microparticulate system, which contains the microparticles that are administered by the method defined by claim 23. Dependent claims 42-44 generally correspond with claims 24-26. Therefore, claim 40 and its dependent claims, claims 41-44 are non-obvious.

Claim 46

New dependent claim 46 depends from claim 26 and specifies that the drug is insulin. Support for claim 46 can be found in the specification at least at page 18, line 33. The Examiner previously indicated that claim 26 was allowable. Therefore new dependent claim 46 is also allowable.

Claims 47-49

New independent claim 47 defines a cartridge for insertion into an inhaler containing microparticles having a size range of between 0.5 and ten microns comprising a drug to be delivered by inhalation and a diketopiperazine, wherein the microparticles release the drug at a pH of 6.0 or greater. Claim 48 depends from claim 47 and further defines the drug as selected from a list of drugs. Claim 49 depends from claim 48 and specifies that the drug is insulin. Support for claims 47-49 can be found in the specification at least at page 5, lines 4-5; page 6, line 2; page 18, lines 5-8, 14-15, and 17-20; page 18, line 32 until page 19, line 3, and page 22, lines 31-32 and page 23, lines 3-6 and 20-23.

As noted above, Boyes discloses microparticles formed of particular wall-forming materials and a surfactant, which encapsulate a drug to be delivered. Boyes discloses particular materials that are suitable to form the microparticles. Boyes does not disclose or suggest using diketopiperazines.

Further, the Examiner indicated that claim 23 and its dependent claims, claims 24-26, were allowable. Claim 47 defines a cartridge for insertion into an inhaler, which contains the microparticles that are administered by the method defined by claim 23. Dependent claim 48 generally corresponds with claim 26; and claim 49 further defines the drug as insulin. Therefore, claim 47and its dependent claims, claims 48 and 49 are non-obvious.

Claims 50 and 51

New independent claim 50 defines a cartridge for insertion into an inhaler containing microparticles having a size range of between 0.5 and ten microns comprising a drug to be delivered via inhalation, wherein the microparticles consist essentially of the drug and a material selected from the group consisting of poly(hydroxy acids), polyanhydrides, polyesters, polyamides, polycarbonates, polyalkylenes, polyvinyl compounds, polysiloxanes, polymers of acrylic and methacrylic acids, polyurethanes and co-polymers thereof, poly(butyric acid), poly(valeric acid), poly(lactide-co-caprolactone), polysaccharides, and copolymers and mixtures thereof, and wherein the microparticles release the drug at a pH of 6.0 or greater. Claim 51 depends from claim 50 and further defines the drug as selected from a list of drugs. Support for claims 50 and 51 can be found in the specification at least at page 5, lines 4-5; page 6, lines 2, 4-6, 8, 12, 13, 20, 29-32; page 18, lines 5-8, 14-15, and 17-20; page 18, line 32 until page 19, line 3, and page 22, lines 31-32 and page 23, lines 3-6 and 20-23.

As noted above with respect to claims 27, 31, 32, and 36, Boyes requires the presence of a surfactant in addition to the wall forming material to delay release of the drug from the microparticle (*see e.g.* page 2, lines 37-41). Boyes explains that a problem with other inhalable formulations was that the drugs were rapidly systemically absorbed, and such formulations were not suitable for the treatment of the diseases of the respiratory system (*see* page 2, lines 7-10). In contrast, claim 50 specifies that the microparticles consist essentially of the drug and a material selected from the listed materials. Therefore claim 50 excludes the incorporation of a surfactant

at a level that delays release of the drug from the microparticle. Boyes teaches away from such microparticles. Claim 51 incorporates the limitations of claim 50, from which it depends. Therefore, claims 50 and 51 are non-obvious in view of Boyes.

Claims 52-54

New dependent claims 52-54 depend from claim 16 directly or indirectly. Claim 52 defines the drug as selected from the drugs listed in claims 26, 31, and 36. Claims 53 and 54 specify that the drug is insulin. Support for claims 52-54 can be found in the specification at least at claim 11 as originally filed and at page 18, line 33. Claims 52-54 depend directly or indirectly from independent claim 16, which has been amended to specify that the material used to form the microparticles may be alginate, chitosan, a hydrophilic or hydrophobic protein, or a lipid. As indicated by the Examiner, Boyes does not disclose or suggest microparticles formed from the listed materials. Therefore, claims 52-54 are non-obvious in view of Boyes.

Additional Amendments to the claims

Claims 28-30 and 33-35 have been canceled in view of the amendments to claims 27 and 33 from which they depend, respectively. Independent claims 16, 22, 23, 27, and 32 have been amended for consistency to refer to release at a "pH of 6.0 or greater". Support for this amendment can be found in the specification at least in claim 1 as originally filed. Claims 18-20 have been amended to refer to "microparticles" in place of "microparticle". Claim 23 has been amended to refer to delivery of an active agent. Claims 23, 27 and 32 have been amended to specify that the microparticles are in or administered from a dry powder inhaler or a container for

a dry powder inhaler. Support for this amendment can be found in the specification at least at page 22, lines 31-32 and page 23, lines 3-6 and 20-23. Claims 27 and 32 have been amended to correct a typographical error by deleting "poly(butic acid)" from the list of materials and replacing it with "poly(butyric acid)". Claims 27 and 32 have been further amended to insert "and" before "copolymers".

Allowance of claims 16, 18-20, 22-27, 31, 32, and 36-54, as amended, is respectfully solicited.

Respectfully submitted,

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